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Severe Metabolic Acidosis in Adult Patients with Duchenne Muscular Dystrophy

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Established Facts

- Long-term ventilation has improved the quality of life and prognosis of patients with Duchenne muscular dystrophy (DMD), but with prolonged survival, previously unrecognized complications can emerge.

Novel Insights

- We observed an unexpectedly high incidence of severe metabolic acidosis in DMD patients of 20–36 years of age, in association with chronic constipation, a reduction of fluid and food intake and respiratory infection. Fluid resuscitation, nutrition, regulation of bowel movements and administration of antibiotics led to rapid recovery in all patients, suggesting that progression to a life-threatening condition may be prevented if this particular risk is recognized and appropriate treatment is established at an early stage.

Key Words
Duchenne muscular dystrophy · Metabolic acidosis · Positive pressure ventilation · Constipation

Abstract
Duchenne muscular dystrophy (DMD) leads to progressive paresis, respiratory failure and premature death. Long-term positive pressure ventilation can improve quality of life and survival, but previously unrecognized complications may arise. We analyzed the characteristics of severe metabolic acidosis occurring in 8 of 55 DMD patients, of 20–36 years of age, observed over a 5-year period. All patients were on positive pressure ventilation and were being treated for chronic constipation. Before admission, they had had a reduced intake of fluids and food. Upon examination, they were severely ill, dyspneic and suffering from abdominal discomfort. Metabolic acidosis with a high anion gap was noted in 5 of

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the 8 patients and with a normal anion gap in the other 3. They all recovered after the administration of fluids and nutrition, the regulation of bowel movements and treatment with antibiotics, as appropriate. Metabolic acidosis is a life-threatening, potentially preventable complication in older DMD patients. Early recognition, subsequent administration of fluids, nutrition and antibiotics and regulation of bowel movements seem to be essential.

Introduction

Duchenne muscular dystrophy (DMD) is the most common form of the inherited muscular dystrophies affecting approximately one in 3,300 male births. The disorder is caused by mutations in the gene located at Xp21, which codes for the dystrophin protein [1]. DMD leads to progressive muscular weakness, tetraparesis with loss of ambulation and chronic respiratory failure at around the age of 9, 14 and 20 years, respectively [2, 3]. Long-term mechanical ventilation improves quality of life and has increased the life expectancy to approximately 35 years [4]. With prolongation of life, previously unrecognized DMD complications can arise. Over the last few years, we observed an unexpectedly high incidence of severe, life-threatening metabolic acidosis in a cohort of adult DMD patients. The purpose of this report is to describe the clinical presentation, potential causes and treatment of the affected patients in order to promote awareness of this potentially preventable complication.

Case Series

The Pulmonary Division at the University Hospital of Zurich provides medical services to a cohort of DMD patients. This includes a yearly clinical examination, blood gas analysis, spirometry and general medical care. Patients are referred to other specialists as needed. All of the patients reside and/or attend school or work in a long-term care facility specialized in muscular dystrophy care, the Mathilde Escher Heim [3, 4]. Patients attending our clinic are at least 16 years old. From February 2005 to November 2010, 8 of the cohort of 55 patients were admitted to the emergency room of our hospital with severe metabolic acidosis, and these 8 represent the study group. Their medical records were analyzed retrospectively with the approval of the hospital ethics committee.

The clinical characteristics and laboratory results of the patients are presented in table 1. At admission, all 8 patients (during 9 episodes of admission) suffered from dyspnea, despite assisted ventilation by mask (n = 7) or tracheostomy (n = 1). They reported abdominal discomfort and distension. All were on long-term treatment for chronic constipation with laxatives and enemas. In 5 patients, this treatment had been intensified on the days before admission. All patients had reduced their food and fluid intake 1–5 days before admission. Two patients presented with recent-onset cough and purulent sputum. Clinical examination revealed that all the patients were in a severely reduced general condition with tachycardia (median 130 beats/min, range 96–156), a mean arterial blood pressure of 93 mm Hg (range 75–103) and a median body temperature of 37.5°C (range 36.5–40.0). The laboratory results at admission on assisted ventilation and supplemental oxygen titrated to maintain SpO_2 >90% are listed in table 1. The arterial pH and bicarbonate were low. The anion gap was elevated in 5 of the 9 episodes of admissions. Urinary ketones were qualitatively positive in all the cases. Further details of the individual acid-base disorders are listed in table 1. Patients with a high anion gap metabolic acidosis combined with bicarbonate loss and ketoacidosis had the lowest pH, despite hyperventilation. The median left ventricular ejection fraction measured in the 8 patients by echocardiography was 52% (range 33–60) with values <55% in 5 cases. Rehydration, parenteral and/or enteral nutrition, pharmacological regulation of intestinal motility and administration of antibiotics led to a complete recovery in all patients. Due to the severity of the acidosis, case 1 received bicarbonate infusions and case 2 needed hemofiltration. Six patients received vitamins and substitution of micronutrients. The pH normalized within 12–48 h (mean 36 h and SD 12 h) and clinical improvement occurred within 2–4 days (mean 2.3 days and SD 1.0 days). The length of hospital stay was 3–38 days.

Discussion

We describe a case series of 8 DMD patients requiring emergency care for severe metabolic acidosis. This condition has, to our knowledge, not yet been described as a common complication in DMD patients. As some of the factors that contributed to the life-threatening condition of these patients can be prevented if recognized early, it is important for physicians to be aware of this potential risk.

A combination of factors led to a severe acidosis in the patients with the lowest pH. The typical causes of metabolic acidosis were ketoacidosis in katabolic states due to acute disease exacerbation and fasting, low bicarbonate because of intestinal loss and inadequate ventilatory compensation. There was no lactacidosis or indication of intoxication to explain the severe acidosis [5–8]. Several potential pathophysiological mechanisms discussed below might have been responsible for the metabolic acidosis in the patients described.

In our experience, many adult DMD patients suffer from chronic constipation and require regular use of laxatives and enemas [9]. This promotes metabolic acidosis by intestinal loss of bicarbonate. The reasons for chronic constipation are not fully understood, but immobility seems to play a role. Furthermore, the lack of dystrophin

Table 1. Clinical patient characteristics and laboratory data

Clinical presentation	Arterial blood gas analysis	K^+ mmol/l	Cl^- mmol/l	AG mmol/l	Lactate mmol/l	CRP mg/l	Urinary Ketone	Acidotic disorder and suspected mechanism
Case 1 Age: 27 years DID: 73 PPV: 24 h/day by mask Acute megacolon	pH 7.03 $PaCO_2$ 28 mm Hg HCO_3^- 8.6 mmol/l	4.3	117	23.4	0.6	125	++	combined high anion gap hyperchloremic acidosis combined with moderate ketoacidosis due to insufficient caloric intake, intestinal bicarbonate loss and dehydration
Case 2 Age: 20 years DID: 69 PPV: 24 h/day by mask Hypoalimentation	pH 7.04 $PaCO_2$ 17 mm Hg HCO_3^- 4.4 mmol/l	3.2	103	37.6	1	21	++++	high anion gap metabolic acidosis with adequate bicarbonate compensation, and ketoacidosis due to insufficient caloric intake
Case 3.1 Age: 27 years DID: 69 PPV: 24 h/day, by trach Hypoalimentation	pH 6.98 $PaCO_2$ 24 mm Hg HCO_3^- 5.7 mmol	3.8	103	26.3	0.8	119	+++	high anion gap metabolic acidosis with adequate bicarbonate compensation, ketoacidosis due to insufficient caloric intake, plus possible D-lactate acidosis
Case 3.2 Age: 31 years DID: 72 PPV: 24 h/day by trach Pneumonia	pH 7.02 $PaCO_2$ 26 mm Hg HCO_3^- 6.5 mmol	3.9	110	8	0.7	333	+++	normal anion gap hyperchloremic metabolic acidosis and ketoacidosis due to infection with dehydration and bicarbonate loss
Case 4 Age: 22 years DID: 67 PPV: 8 h/day by mask Viral gastroenteritis	pH 7.01 $PaCO_2$ 18 mm Hg HCO_3^- 5.4 mmol	3.3	112	23.6	0.7	77	++++	combined high anion gap hyperchloremic metabolic acidosis, ketoacidosis due to insufficient caloric intake, intestinal bicarbonate loss and dehydration
Case 5 Age: 36 years DID: 76 PPV: 24 h/day by mask Acute megacolon	pH 7.29 $PaCO_2$ 19 mm Hg HCO_3^- 9.1 mmol	2.5	118	11.9	0.5	28	++	normal anion gap hyperchloremic metabolic acidosis due to intestinal bicarbonate loss and dehydration
Case 6 Age: 21 years DID: 62 PPV: 8 h/day by mask Pneumonia	pH 7.26 $PaCO_2$ 51 mm Hg HCO_3^- 21.9 mmol	3.4	101	14.1	0.7	125	++++	high anion gap normochloremic combined metabolic and respiratory acidosis, dehydration
Case 7 Age: 28 years DID: 76 PPV: 8 h/day by mask Acute megacolon	pH 7.17 $PaCO_2$ 50 mm Hg HCO_3^- 16.3 mmol	4.4	114	11.7	0.4	196	+++	normal anion gap hyperchloremic combined metabolic and respiratory acidosis, moderate ketoacidosis and intestinal bicarbonate loss
Case 8 Age: 24 years DID: 71 PPV: 24 h/day by mask Acute cholecystitis	pH 7.29 $PaCO_2$ 31 mm Hg HCO_3^- 14.4 mmol	3.6	113	12.7	1.5	122	+++	normal anion gap hyperchloremic metabolic acidosis, intestinal bicarbonate loss

AG = Anion gap; CL^- = serum chloride concentration; CRP = serum C-reactive protein concentration; DID = Duchenne Muscular Dystrophy Physical Impairment and Disability score ranging from 9, no disability to 80, complete dependency on care [4]; K^+ = serum potassium concentration; lactate = serum lactate concentration; PPV = positive pressure ventilation; trach = by tracheostomy; urinary ketone = qualitative ketone concentration.

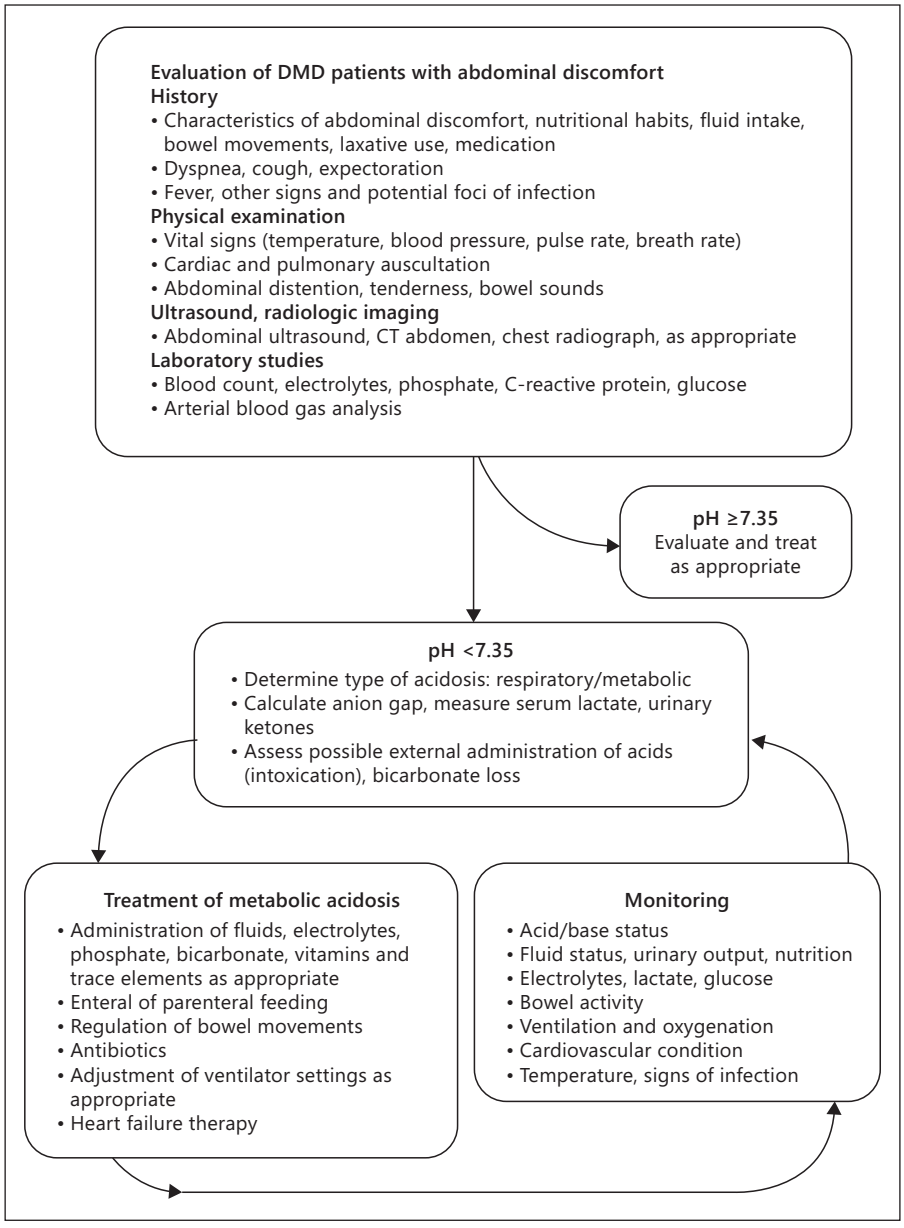

Fig. 1. Flowchart for assessment and treatment of patients with DMD admitted to the hospital with abdominal discomfort. Of note, this chart focuses on metabolic acidosis and does not provide a comprehensive account of all necessary assessments and treatments.

as an anchor for nitric oxide synthase is a possible cause of low intestinal nitric oxide levels and therefore may impair intestinal relaxation [10–12]. Chronic dysmotility may also lead to intestinal bacterial overgrowth, a risk factor for D-lactacidosis. In this study, D-lactacidosis was evaluated only in patient 8, although it was suspected in case 3 at the first admission because of the extremely low pH recorded, which was not fully explained by the measured ketone bodies. Starvation and katabolic metabolism due to acute infection predisposes to ketoacidosis. Moreover, dehydration may have led to diminished urine output and to reduced excretion of titrable acids such as beta-hydroxybutyrate. This may have promoted constipation and led to the laxative therapy. Available data suggest that several of the discussed causes of metabolic acidosis may have been relevant in our case series (table 1). We found both high anion gap acidosis (cases 1, 2, 3.1, 4 and 6) and normal anion gap acidosis (cases 3.2, 5, 7 and 8). It appears that the severe metabolic acidosis with a pH <7.05 in cases 1–4 was due to a combination of factors including ketoacidosis. Moderate metabolic acidosis with a pH of approximately 7.25–7.3 was related to the gastro-

intestinal loss of bicarbonate from diarrhea or after forced laxative therapy by enema in cases 5–8. As most of the patients had impaired left ventricular function consistent with cardiomyopathy, congestive heart failure may have aggravated the metabolic acidosis. Serum lactate levels were not elevated, however.

Our observations in older DMD patients on long-term ventilation demonstrate that severe metabolic acidosis related to chronic constipation and its treatment as well as reduced fluid and food intake and associated respiratory infection constitute a previously unrecognized complication of DMD. The result may be a life-threatening condition. We suggest that immediate administration of adequate amounts of fluid and nutrition, the regulation of bowel movements and treatment with antibiotics, as appropriate, might be essential for the prevention and treatment of this condition. A flow-chart with the suggested practical management is shown in figure 1. We recommend that patients with DMD or other advanced neuromuscular diseases predisposing to serious complications such as those described here are referred for treatment in specialized centers.

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